

Global monkeypox outbreak 2022: First case series in Singapore

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ABSTRACT

Monkeypox is a global health emergency. Prior to 2022, there were few reports of monkeypox outside of endemic countries, which were mostly travel-related. Since May 2022, an exponential increase in monkeypox infections in previously non-endemic countries has been reported. Unlike previous outbreaks of monkeypox, which were zoonotically transmitted and presented with generalised vesicular eruptions after prodromal symptoms, cases of the current outbreak feature significant travel and sexual history, and atypical localised genital eruptions with unpredictable onset relative to viral prodrome-like symptoms. We summarise the 15 Singapore cases reported to date as of August 2022, and highlight salient clinical clues that may aid physicians in narrowing the broad differential diagnosis of an acute vesicular genital eruption. Although research into vaccination and antiviral strategies is ongoing, monkeypox is currently conservatively managed. Clinical vigilance and a high index of suspicion are required to facilitate early detection and isolation of cases to contain transmission in Singapore.

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INTRODUCTION

Monkeypox has been declared a public health emergency of international concern. Up until 2022, most cases of monkeypox have been reported in parts of Africa. On 7 May 2022, a returning traveller from Nigeria to the UK was confirmed to have contracted monkeypox. By the end of May 2022, 23 countries had reported cases of monkeypox to the World Health Organization (WHO), and many of these cases did not involve a recent visit to an endemic country. On 23 June 2022, WHO convened a meeting of the International Health Regulations (2005) Emergency Committee on the multinational monkeypox outbreak this year, bringing global attention to this disease.¹

The monkeypox virus is a member of the *Poxviridae* family, genus *Orthopoxvirus*. There are 2 genetically distinct clades—the West African clade and the Basin clade (Central African). Transmission in endemic areas was largely zoonotic via consumption of uncooked small mammals and contact with diseased animals through impaired skin barrier or respiratory route, while human-to-human transmission through household

contacts were observed in outbreaks.²⁻⁵ Conventional signs included fever, chills, pharyngitis, conjunctivitis, generalised vesiculo-pustular eruption, and potential progression to pulmonary failure and encephalitis. A mortality rate of approximately 1% for the West African clade and up to 10% for the Congo Basin clade was observed; victims were predominantly children aged 3–5 years.^{3,4} In 2003, an outbreak of 47 zoonotically transmitted monkeypox infections with household transmissions was reported in the US. Infected prairie dogs that had been temporarily kept in the vicinity of imported monkeypox-infected wild-caught rodents from Ghana were identified as the culprit animal reservoirs. Symptoms were similar to those observed in Africa. In this outbreak, however, there were no reported mortalities or interhuman transmissions.⁵⁻⁷

The first case of monkeypox in Singapore was diagnosed in 2019. A business traveller from Nigeria had presented with fever, chills, myalgia and a generalised pustular eruption. Infection was attributed to the consumption of contaminated bushmeat in Ebonyi State 2 weeks prior. Close contacts were quarantined, and

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CLINICAL IMPACT

What is New

- The current monkeypox epidemic differs from classic monkeypox in risk factors, transmission, clinical presentation and outcome.
- Travel and sexual history are important potential risk factors.
- Localised anogenital vesiculo-pustules are a common presentation in the current outbreak, and may occur unpredictably relative to other viral prodrome-like symptoms.

Clinical Implications

- Alternative diagnoses that may fully explain the symptoms should be excluded clinically or via point-of-care testing if available.
- A high index of suspicion should be maintained in such situations.

vaccination with smallpox live vaccine (ACAM2000, Emergent Product Development Gaithersburg Inc, Gaithersburg, US) was offered and administered to 14 people without serious adverse events. There was no local transmission and no further local cases of monkeypox until the current outbreak in 2022.⁸

Since the onset of the monkeypox outbreak this year, 15 cases of monkeypox have been diagnosed in Singapore as of 10 August 2022. Measures such as case isolation and contact tracing have been enforced to contain local transmission. As Singapore relaxes travel restrictions that were instituted during the COVID-19 pandemic, more cases of monkeypox are likely to be diagnosed in the country. The current monkeypox outbreak has demonstrated significant interhuman transmission of the disease, with clinical presentations that differ from those of previous outbreaks, emphasising the need to update our understanding of this evolving disease. We summarise the 15 local cases based on the Ministry of Health (MOH), Singapore's situation update,⁹ and discuss factors that may differentiate monkeypox from other clinical differentials of an acute vesicular genital eruption.

Diagnosed cases to date in Singapore

All 15 diagnosed cases of monkeypox infection in Singapore (Table 1)⁹ were male adults of 25–54 years (median 36 years, mean 38.4 years, interquartile range 15 years). Five cases had a positive history of travel and sexual contact in a country with reported monkeypox

cases. Details regarding symptoms of the last 4 cases were not reported. Six of the first 11 cases developed skin lesions first, 5 of whom were located on the inguinal and anogenital regions, and the last on the lower abdomen. One of these 6 cases had concurrent anogenital and extragenital skin lesions as a first symptom, while the rest had more localised lesions. The other 5 patients initially developed fever (sole symptom in 2, accompanied by headache, anal discomfort and myalgia in 1), headache alone (n=1), or anal discomfort alone (n=1). All of the first 11 patients subsequently developed skin lesions in the course of their disease. Putting aside the time of appearance of skin lesions, 5 patients had skin lesions in the anogenital area; 3 had anogenital and extragenital skin lesions; 1 had anogenital and extragenital skin lesions localised to the lower abdomen; and 2 had lesions on unspecified locations. Additionally, 8 cases were reported to have fever and 2 were reported to have lymphadenopathy. These reported symptoms are based on MOH local situation update,⁹ which may not accurately reflect the full range of symptoms experienced by these patients throughout the course of the disease as these reports are made only upon first confirmation of diagnosis.

Table 1 summarises the presentations of the diagnosed cases in Singapore since the start of the global monkeypox outbreak this year. Representative lesions from one of these cases are depicted in Fig. 1, demonstrating vesicles, pustules, erosions and scabs occurring contemporaneously.

DISCUSSION

Clinical features of the current outbreak versus classic monkeypox

It has been highlighted that the clinical features of the current monkeypox outbreak differ from those reported in the classic version, in terms of mode of transmission, demographics of at-risk persons, sequence of symptom onset, morbidity and mortality.^{10–12} Monkeypox infection, as described in outbreaks prior to 2022, had an incubation of 7–17 days. The disease was heralded by a prodrome of fever, headache, fatigue, malaise, backache, and severe localised or generalised lymphadenopathy. Patients developed skin lesions 1–3 days after the prodrome, usually starting as a synchronous maculopapular eruption with lesions of 2–5mm diameter, with centrifugal spread. The lesions became papular, vesicular, pustular and then crusted over the next 2–4 weeks, resolving with scarring and pigmentary change.^{13,14}

The current outbreak of monkeypox differs in terms of epidemiology and clinical features. Firstly, a large proportion of cases occurring in non-endemic countries

Table 1. Summary of locally reported cases to date

n=15	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Age	42	45	36	30	48	41	46	26	31	28	32	59	33	25	54
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Travel history	Yes, location not reported	No	Yes, US	Yes, Germany	No	No	Yes, London	No	No	Yes, Canada	No	No	No	No	No
First symptom	Headache	Rash on lower abdomen	Anal discomfort	Groin rash	Perianal rash	Genital rash	Groin rash	Rash on genital region and other body regions	Fever	Fever, headache, anal pain and myalgia	Fever	Unreported	Unreported	Unreported	Unreported
Rash	Yes, location not reported	Yes, lower abdomen	Yes, rashes “typical of monkeypox”	Yes, groin rash	Yes, perianal rash	Yes, genital rash	Yes, groin rash	Yes, genital rash and rashes in other body regions	Rashes on face, perianal region that spread to other body parts	Yes, perianal rash	Yes, genital rashes that spread to other body regions	Unreported	Unreported	Unreported	Unreported
Fever	Yes	Yes	Unreported	Yes	Yes	Unreported	Yes	Unreported	Yes	Yes	Yes	Unreported	Unreported	Unreported	Unreported
Lymphadenopathy	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Sore throat	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Fatigue	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Other symptoms	Unreported	Unreported	Yes, not specified	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported

Source: Ministry of Health, Singapore. Monkeypox. Available at: <https://www.moh.gov.sg/diseases-updates/monkeypox>. Accessed on 13 August 2022.



Fig. 1. Representative lesions from a locally diagnosed case demonstrating contemporaneous lesions at various stages of development.

- (A) Epithelialising ulcer at the base of shaft of penis with another ulcer on pubis.
- (B) Small vesicle on an erythematous base on the palmar aspect of the left 5th finger.
- (C) Eroded vesiculo-pustule on an erythematous base over the right supraclavicular region.
- (D) Close-up of a representative umbilicated pustule on an erythematous base.

are reported among men who had recent sexual interactions with a new male partner or multiple partners. Secondly, many cases had only a few lesions, which could be localised to the genital area including mucosal surfaces, and appear without prodrome. Lesions were asynchronous, and the presence of lesions at different stages of evolution was observed in some patients.¹⁵ Some patients, on the other hand, did not have rashes. Anal pain and anal bleeding were other features different from the classic presentation. Associated symptoms such as fever, myalgia, fatigue, headache, sore throat and lymphadenopathy were common throughout the course of the disease, but the sequence of symptomatology varied.^{15,16}

Case definition of suspected monkeypox

Given the varied presentation of the current monkeypox outbreak, the initial local guidance for defining a suspect case was relatively broad, casting a wide net to pick up possible cases (MOH Circular No. 63/2022, 20 May 2022).¹⁷ Doctors were instructed to notify possible cases if they had fever, acute vesicular rash, and either a travel history to countries with reported monkeypox cases

or a history of close contact with an infected person within 21 days before the onset of symptoms. This led to reports of cases where there was a clear probable alternative diagnosis for the symptoms.¹⁷

The latest Singapore guidance of when to suspect monkeypox (MOH Circular No. 79/2022, 1 July 2022)¹⁸ reflects our evolving understanding of the current outbreak and refines the suspect case definition. Risk factors and clinical features taken into consideration in the current guidance include recent travel history to countries with confirmed cases of monkeypox, history of close contact (sexual or non-sexual) with an infected person or within a network with circulating monkeypox activity, an unexplained acute rash and constitutional symptom(s). Clinicians were additionally reminded to exercise clinical judgment to exclude other common conditions that may present similarly, such as varicella zoster virus (VZV), herpes zoster virus (HZV), enteroviral infections e.g. hand-foot-mouth disease (HFMD), measles, herpes simplex virus (HSV), other sexually transmitted diseases (STDs), molluscum contagiosum, dengue, and dermatitic conditions. Supplementary Table S1 (in the online version of this article) compares the Singapore suspect case definition to that used in selected other countries, which are relatively similar.

Disease mimics

It may be difficult for the clinician to differentiate potential causes of an acute rash in individuals with exposure history who become symptomatic, with compatible constitutional symptoms. A thorough history and examination, tailored to the patient's demographics and medical history, will provide clues to arriving at the correct diagnosis.

The majority of cases reported in this outbreak have been in men who have sex with men (MSM) who have recent sexual exposure, therefore STDs rank highly on the list of differentials and may also occur concomitantly.¹⁶ The first is HSV infection.

Patients with HSV infection have tender, grouped vesicles or shallow erosions with an erythematous border. These may be preceded by a prodrome. When more severe, patients may have adjacent lymphadenopathy. Immunocompromised patients may present with more severe signs and constitutional symptoms, hence human immunodeficiency virus (HIV) tests should be performed in all patients who are not already known to have HIV. A swab for HSV polymerase chain reaction (PCR) should be taken. If available, a Tzanck test can be performed but may not differentiate between different *Herpesviridae* infections such as HSV, VZV or HZV.

The chancre of primary syphilis is classically described as a single painless ulcer with firm edges. Patients may have more than one chancre. Unlike monkeypox lesions, syphilitic chancres do not evolve through stages of tender vesicle or pustule, but are papules that ulcerate. Secondary syphilis in some cases may be difficult to differentiate from the vesiculopustular eruption of monkeypox. Pustular secondary syphilis is rare, estimated to occur in approximately 1.9% of patients with secondary syphilis.¹⁹ Dark-field microscopy of skin lesions will demonstrate spirochetes of *Treponema pallidum* in moist lesions and can be a useful rapid test in a clinic with appropriate resources. A rapid plasma reagin test should be performed for all patients with anogenital ulcers. It is often positive in primary syphilis and always positive in secondary syphilis.

Disseminated gonococcal infection (DGI) is another important differential. Patients may develop oligoarticular septic arthritis, arthralgia, fever, and systemic complications such as meningitis and endocarditis. Petechial or pustular lesions are usually acrally distributed. Gram stain, culture and nucleic acid amplification test (NAAT) from swabs of pustular skin lesions or synovial fluid in suspected DGI are not sensitive.^{20–22} Although the primary site of infection may not be clinically apparent, it is still advisable to obtain samples from all reported sites of sexual exposure. The gold standard investigation is a NAAT for *Neisseria gonorrhoea* from first-void urine, urethral discharge or secretions.²³

Lymphogranuloma venereum (LGV), chancroid and granuloma inguinale are rarely diagnosed STDs in Singapore, but should also be considered when evaluating a patient with fever, genital lesions, and a compatible exposure history. LGV is similar to monkeypox in having prominent tender lymphadenopathy, but the genital lesion of LGV tends to be a single spontaneously resolving papule/vesicle/ulcer. Chancroid also presents with single or multiple inflamed genital papules that progress into painful ulcers, together with tender inguinal lymphadenopathy. Gram stain, albeit again insensitive, may demonstrate strands of Gram-negative rods in a “school of fish” appearance. The lesions of granuloma inguinale are characteristically beefy red, painless, slowly progressive genital ulcers without regional lymphadenopathy.^{23,24}

Non-STDs that may present with a vesicular eruption on the anogenital area include VZV, enteroviral infections, HZV and impetigo. Both VZV and enteroviral infections may be preceded by a mild

prodrome and have an oral enanthem. In VZV, there is a cephalocaudal spread of vesicles on an erythematous base, characteristically with lesions at different stages presenting simultaneously, and usually sparing the distal limbs and lower limbs. An example of enteroviral infection is HFMD, which presents with oral stomatitis and acral vesicles that may become generalised. HFMD is more common in children, although adults may also be affected. HZV that affects the S1–S3 dermatome may present with grouped vesicles that coalesce into bullae and erosions with scalloped borders over the anogenital region. Clues to this diagnosis include a preceding sensation of hyperaesthesia or hyperalgesia in the corresponding dermatome, and unilateral lesions that respect the midline. As aforementioned, Tzanck smear may be useful to support *Herpesviridae* infection as a point-of-care test, but lesional swabs for PCR for VZV, enteroviruses, and HSV should be obtained for confirmation of diagnosis. Impetigo is recognised by presence of golden crusting on erythematous erosions, typically over the face and extremities. It may be a primary cause of anogenital pustulation, or a secondary infection of pre-existing lesions of other causes. Pyogenic culture from lesional swab should be obtained to guide treatment.²⁴

Lastly, insect bite reactions may give rise to pruritic, urticated papules that can progress to vesiculobullae or persistent prurigo nodularis-like lesions. The bites may correspond to sites of exposure, and a history of environmental exposures, pets and hobbies can be revealing. Some patients may develop a hypersensitivity reaction in the form of papular urticaria that can be generalised; lesions tend to be more urticated and erythematous rather than pustular, unless there is a secondary infection.²⁴

Table 2 compares and contrasts selected differentials of monkeypox eruption.

Diagnosis of monkeypox

Monkeypox diagnosis can be made via NAAT. Singapore uses specific monkeypox virus (MPXV) PCR, which is preferable to the less specific *Orthopoxvirus* PCR. Genetic sequencing to determine the virus clade is recommended by WHO. Suitable samples include a vigorous swab of exudate or lesion, roof of lesion, or crusts. Sampling should be performed from at least 2 lesions of the same type, preferably of different appearance and at different locations of the body. Lesions of different types (e.g. exudate vs skin vs crust) should be collected in different tubes of viral transport media. Samples should be refrigerated at 2–8°C or frozen

Table 2. Selected differentials of current monkeypox outbreak^{22,24,25,29}

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Monkeypox (current outbreak)	- Lesions at same stage of development, localised or generalised, frequently genital distribution - Sequential development from macules to papules to vesicles to pustules to scabs over 2–4 weeks - Papulovesicular/pustular stage consists of deep-seated discrete or grouped lesions, often with umbilication	- Tender lymphadenopathy - Viral prodrome-like symptoms may occur before, together or after onset of rash - May have anal discomfort	- Lesions were classically described to be at the same stage of development, although asynchronous lesions have been reported in the current outbreak - Epidemiologic risk factors in terms of travel, sexual history, and contact with dead/live African endemic exotic species	- Sequence of symptom onset is variable - Cases may not have relevant exposure history - May be clinically indistinguishable from less common presentations of SARS-CoV-2 infection or secondary syphilis, or atypical presentations of the other listed differentials	- Lesional swab for MPXV PCR - Consider opportunistic screening for other STIs, including syphilis (such as POC testing with RPR) and HIV (POC)
Herpes simplex	- Grouped vesicles on an erythematous base that may coalesce into bullae/erosions with scalloped borders - Can range from asymptomatic to excruciatingly painful	- Viral prodrome before onset of lesions - May be associated with regional lymphadenopathy	Characteristically grouped lesions with scalloped border on erythematous base, unlike monkeypox lesions which can be discrete	- Similar sexual epidemiologic risk factor to monkeypox - Monkeypox may also have grouped vesicles on an erythematous base indistinguishable from HSV	- Lesional swab for Tzanck smear (POC) - Lesional swab for HSV PCR
Disseminated gonococcal disease	Acral distribution of petechial or pustular eruptions	- Milky white or purulent discharge from exposed infected areas e.g. urethra, rectum, vagina, oropharynx - Fever - Arthralgia - Oligoarticular septic arthritis - May have complications such as perihepatitis, meningitis, pelvic inflammatory disease, endocarditis	- Genital discharge is not a feature of monkeypox - Swollen and tender oligoarthritis if septic gonococcal arthritis - Pustules do not demonstrate umbilication	- Similar sexual epidemiologic risk factor to monkeypox - Gram stain of pustules is not sufficiently sensitive to rule out gonococcal infection	<i>Neisseria gonorrhoeae</i> PCR from relevant sites <i>Neisseria gonorrhoeae</i> culture
Lymphogranuloma venereum (LGV)	- Causative organism: the L1, L2 and L3 serovars of <i>Chlamydia trachomatis</i> - Primary lesion seen in up to half of cases (1st stage of LGV) — herpeticiform lesion that spontaneously resolves without scarring	- Constitutional symptoms are rare - Inguinal syndrome (second stage of LGV): suppurative unilateral inguinal lymphadenopathy with overlying erythema - Anogenito-rectal syndrome (3rd stage of LGV): proctocolitis, perirectal abscesses, urogenital fistulas	- Inguinal lymphadenopathy can be suppurative in LGV - LGV does not usually have multiple vesicles/pustules	- Similar sexual epidemiologic risk factor to monkeypox - Both LGV and monkeypox may cause tender lymphadenopathy - Monkeypox may rarely have no rash or only a single lesion	- Serological tests i.e. LGV complement fixation test - Culture from lymph node aspiration <i>Chlamydia trachomatis</i> PCR from urine as well as other clinical sites as appropriate
Chancroid	- Causative organism: <i>Haemophilus ducreyi</i> - Single to multiple painful, purulent and deep genital ulcers with well-defined soft undermined edges	- Painful suppurative inguinal lymphadenopathy (buboes) - Scarring from recurrent buboes may result in urogenital or rectal fistulas	- Inguinal lymphadenopathy can be suppurative in chancroid - Ulcers in chancroid tend to be larger and deeper compared to the shallower erosions of ruptured vesicles and pustules in monkeypox	- Similar sexual epidemiologic risk factor to monkeypox - Both chancroid and monkeypox may cause tender lymphadenopathy	- Smear for direct microscopy (POC, although poor sensitivity) - Culture of smear from ulcer/aspirate from buboes - Smear for PCR

Table 2. Selected differentials of current monkeypox outbreak^{1,2,22,24,25,29} (Cont'd)

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Granuloma inguinale	• Causative organism: <i>Klebsiella granulomatis</i> • Beefy vascular ulcers that began as small papules/nodules which slowly enlarged and ulcerated over weeks to months • Associated with odorous exudate • Subcutaneous granulomas (pseudobuboes) may be present	• Secondary dissemination may lead to involvement of any internal organ or bone	• Granuloma inguinale usually does not have regional lymphadenopathy, while lymphadenopathy is a common feature of monkeypox • Ulcers of granuloma inguinale are large, vascular, and foul smelling, unlike smaller lesions characteristic of monkeypox	• Similar sexual epidemiologic risk factor to monkeypox • Early stage of granuloma inguinale may be mistaken for monkeypox especially when lesions are still small and have not developed the characteristic beefy appearance	• Tissue smear from ulcer for intra-cellular Donovan bodies within histiocytes (not available at all institutions) • Biopsy of ulcer • Culture is difficult with no commercially available PCR
Primary syphilis	• Usually a single painless papule, which may develop into a well-circumscribed surface ulceration that is firm on palpation	• Regional lymphadenopathy	• Primary syphilis is frequently asymptomatic, whereas monkeypox usually has associated prodromal symptoms and tender cutaneous lesions	• Similar sexual epidemiologic risk factor to monkeypox • Chancres may infrequently be multiple and may mimic atypical monkeypox presentations that have few cutaneous lesions	• Lesional smear for darkfield microscopy (POC) • Non-treponemal tests e.g. RPR (POC) • Treponemal tests e.g. TPHA, TPAb • Consider opportunistic screening for other STIs as well, including HIV (POC)
Pustular secondary syphilis	• Miliary pustular syphilis: perifollicular pustules approximately 3–5mm diameter • Acneiform syphilis: acneiform papules and pustules on the face • Varioliform syphilis: umbilicated erythematous infiltrated papules and pustules with superficial erosions • Impetiginoid syphilis and ecthymiform syphilis have lesions similar to impetigo and ecthyma, respectively • Rupoid syphilis: papules and pustules with overlying thick hyperkeratotic crusts resembling oyster shells	• Prodromal symptoms • Lymphadenopathy	• Pustular secondary syphilis is a very rare presentation of syphilis. It is far more common for the rash of secondary syphilis to be a papulosquamous eruption. • There may be a history suggestive of previous primary syphilis	• Similar sexual epidemiologic risk factor to monkeypox • Cutaneous features and prodrome-like symptoms can be indistinguishable from monkeypox	• See above
Varicella zoster	• “Dew drops on a rose petal” appearance, describing clear 1–3mm vesicles with a narrow erythematous halo • Lesions at varying stages concurrently • Cephalocaudal spread • Usually spares distal limbs and lower limbs • Oral enanthem	• Mild viral prodrome • More severe presentation and higher risk of extracutaneous complications in adolescents and adults compared to children	• Lesions are at varying stages concurrently • No previous varicella vaccination or varicella zoster infection	• Generalised vesicular eruption, +/- umbilication may be difficult to differentiate from classic monkeypox eruption	• Lesional swab for Tzanck smear (POC) • Lesional swab for varicella zoster virus PCR

Table 2. Selected differentials of current monkeypox outbreak^{1,2,24,25,29} (Cont'd)

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Herpes zoster	- Grouped vesicles that may coalesce into bullae/erosions with scalloped borders - Dermatomal distribution - May be preceded by hyperaesthesia/hyperalgesia in the corresponding dermatome	Neuropathic symptoms in the associated dermatome (may persist as postherpetic neuralgia)	- Dermatomal in nature - Does not cross midline - History of previous varicella zoster infection	- Disseminated zoster is not confined to the dermatome - Genital zoster is uncommon	- Lesional swab for Tzanck smear (POC) - Lesional swab for herpes zoster virus PCR
Hand-foot-mouth disease	- Acral erythematous vesicles with oral stomatitis - May become generalised, involving the face, perioral areas, trunk, buttocks and extremities	- Mild prodrome - Neurologic, cardiopulmonary complications, and death may occur in young children with hand-foot-mouth disease due to enterovirus 71 infection	- Usually affects young children - Oropharyngeal lesions are frequent, occurring on the tongue, buccal mucosae, palate, uvula, tonsillar pillars - Lesions may be more prominent in areas of pre-existing eczematous dermatitis (eczema coxsackium)	Generalised vesicular eruption may be difficult to differentiate from classic monkeypox eruption	- Usually a clinical diagnosis - Swabs for cell culture or PCR for enterovirus or coxsackievirus can be done if aetiological confirmation is necessary
Impetigo	- Early lesions begin as a single 2–4mm erythematous macule that quickly evolves into a short-lived vesicle or pustule - Late lesions present as superficial erosions with “honey yellow” crust, and direct extension of the infection to the surrounding skin - The less common bullous variant that presents with small vesicles, which then enlarge into superficial bullae (initially 1–2cm, later up to 5cm in diameter); with a collarette of scale after rupture	May also have systemic symptoms like fever, weakness and mild lymphadenopathy	- More common in children - Predilection for face (around the nose or mouth) and extremities - Golden crusting is typical	Less common bullous variant may also affect trunk, buttocks and genitals	Swab lesions for pyogenic culture
Insect bites and insect bite reactions	- Pruritic urticated papules (usually 2–8mm) that may progress to vesiculobullae or persistent prurigo nodularis-like lesions - May develop papular urticaria, a hypersensitivity reaction to the initial bite(s) that can be localised to sites of bites or generalised	- May not have prodromal symptoms - Rarely associated with anaphylaxis	- Papules may have visible punctum - Patterns of eruption tend to correlate with exposure or exposed areas - History of outdoor exposures, pets, work and hobbies	- Patients may also have a travel history - Secondary infection (e.g. Staphylococcal) may appear more pustular	- Parasite smear may sometimes, but not often, yield arthropod parts (POC) - Swab lesions for pyogenic culture for secondary bacterial infection

HIV: human immunodeficiency virus; HSV: herpes simplex virus; LGV: lymphogranuloma venereum; MXPX: monkeypox virus; PCR: polymerase chain reaction; POC: point of care; RPR: rapid plasma regan; STI: sexually transmitted infection; TPAb: *Treponema pallidum* antibody; TPHA: *Treponema pallidum* haemagglutination

Superscript numbers: Refer to REFERENCES

to below -20°C within 1 hour of collection, and transported to the laboratory in triple packaging in accordance with local infectious disease control protocols. WHO recommends that it may be prudent to collect 2 sets of samples, in order to reduce sampling error. The second set may be tested if the first sample yields an inconclusive result.²⁵

Other investigations, such as testing for acute and convalescent serum antibodies against the monkeypox virus, can be done if NAAT is inconclusive, but are not recommended as standalone tests. Viral culture and electron microscopy are currently not recommended for routine diagnostic testing either.²⁵

Management of monkeypox

Prevention

Timely updates to the general public in Singapore are given via the media to educate on the symptoms and transmission of monkeypox and remind the public to practise strict personal hygiene.²⁶ At-risk groups such as MSM are advised by WHO to temporarily reduce the number of sexual partners and to exchange contacts with new partners to facilitate contact tracing.²⁷ Travellers to affected countries should additionally avoid contact with wild animals, and seek medical attention if new symptoms of fever, lymphadenopathy or rashes develop within 3 weeks of return from travel.⁹ Close contacts of infected persons are quarantined and undergo appropriate regular surveillance for the development of symptoms.²⁸

General measures

Supportive management is the current standard of care. This includes attention to wound care to prevent secondary skin infections, analgesics/antipyretics/antiemetics and other symptomatic treatment as necessary, monitoring for systemic complications, and addressing any psychosocial impact in a sensitive manner. Standard, contact, droplet and airborne precautions are currently advised to all persons who attend to confirmed cases of monkeypox.¹⁸ If tolerable, exposed lesions should be covered when others come into the patient's isolation room. Environmental measures include segregation and disposal of infectious waste; machine-washing contaminated linen in hot water $>60^{\circ}\text{C}$ with laundry detergent and drying at high heat; and cleaning contaminated surfaces with detergent and water followed by an approved virucidal disinfectant. Such precautions should continue until all the lesions have scabbed over and all scabs have fallen off revealing intact new skin underneath.²⁹

Pharmacologic treatment

Treatment of monkeypox is largely conservative at present. In the UK, US and Australia, smallpox vaccination has been approved in certain circumstances to reduce the risk of monkeypox. Smallpox vaccines contain the vaccinia virus, which also belongs to the *Orthopoxvirus* genus, and hence provide some cross-protection against monkeypox. The Smallpox Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) is a non-replicating live-attenuated virus suitable for immunosuppressed persons, pregnant or breastfeeding women, children and those with atopic dermatitis. It is available in the UK, US and Australia, and involves 2 subcutaneous injections 4 weeks apart for primary vaccination. Side effects include local injection site reactions, and viral prodrome-like symptoms. ACAM2000 is a live vaccine that is an alternative to MVA-BN in the US and Australia currently. The side effect profile is similar to MVA-BN, but rare serious adverse events such as progressive vaccinia, generalised vaccinia, eczema vaccinatum, severe cutaneous adverse drug reactions, myocarditis, encephalitis, encephalomyelitis, or encephalopathy have also been reported. Furthermore, the vaccination site is an infectious lesion that may result in autoinoculation of other body parts or infection of other people.³⁰⁻³² In Singapore, smallpox vaccination may be offered as a post-exposure prophylaxis in close contacts of a confirmed person with monkeypox, although specific local guidance on eligible individuals is not yet available.²⁸

As to the use of antivirals in confirmed monkeypox infection, WHO recommends that antiviral use be in the context of a randomised clinical trial. Tecovirimat is a p37 viral envelope protein inhibitor with clinical effectiveness against smallpox in animal models. It is administered orally 600mg twice daily for 2 weeks, based on phase 3 placebo-controlled pharmacokinetic and safety trial in humans.^{33,34} It is licensed by the European Medicines Agency for the treatment of monkeypox, but is not approved by the US Food and Drug Administration or the Australian Therapeutic Goods Administration.²⁹ Nonetheless, Australian guidelines recommend considering the use of tecovirimat in those with or at high risk of severe disease (e.g. haemorrhagic complications, sepsis and encephalitis).³⁵ Other potential antiviral treatments that are also currently not approved for use against monkeypox include brincidofovir, cidofovir and NIOCH-14.²⁹ In Singapore, there are no approved antiviral medications for both infected persons and at-risk individuals.

CONCLUSION

Monkeypox is an emerging virus that has the potential to cause significant physical and psychosocial morbidity. Early stages may mimic other common infectious and non-infectious conditions. Moreover, significant variation in clinical presentations of persons infected in the current outbreak, many of whom do not develop the characteristic generalised vesiculo-pustular eruption of previous outbreaks, highlights the need for clinicians to take a detailed travel and sexual history, to maintain a high index of suspicion to detect cases, and isolate cases to prevent onward transmission to contain the local outbreak.

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